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Immunogenicity of Neonatal BCG Vaccination in Children Entering Primary School

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Abstract: This study has been designed to evaluate the immunogenicity of neonatal BCG-vaccination in children at the age of 7 to 8 years, by skin test using Purified Protein Derivative (PPD), as BCG vaccination at birth is a part of routine program of immunization in our country, Iran; we decided to study its efficacy and also tried to determine if there is any correlation between PPD-test results and BCG scar size. This is a comparative study on 150 children (94 males and 56 females) at the age of 7 to 8 years, who possess neonatal-BCG scar. They were chosen from several primary schools in Tabriz-Iran, by simple random sampling and tested with 0.1 mL of 5-unit-PPD solution (a product of Iran Institute of Razi); then observations recorded. The average diameter of BCG scars were 7.03 mm in girls, 5.45 mm in boys and 6.05 for all. The diameter of induration area resulted from PPD-test after 72 h was less than 5 mm in 95.33% and 5-9 mm in 4.66% of studied children; there was no case with induration area of 10 mm or more at all. Every child who developed an induration area of 5 mm or more by PPD test, had a BCG scar with the diameter of 5 mm or more. There was a statistically meaningful direct correlation between sizes of neonatal-BCG scar and diameter of induration area after PPD-test ($r = 0.21$ and $p = 0.008$). This study shows that reactivity to PPD test (and probably immunity against tuberculosis) decreases as age increases; therefore it seems to be necessary to repeat BCG-vaccination in children at the age of entering primary school.

Key words: Tuberculosis, BCG vaccination, PPD test, children

INTRODUCTION

Tuberculosis is the leading cause of death burdened by infectious diseases on the world. It caused 3 million deaths in 1995 which 170,000 of them happened in children whose age was less than 15 years (Botswana, 1996).

At present time one third of world's population are infected by mycobacterium tuberculosis, which is one of the most important factors that threaten world's health.

Control of tuberculosis by chemotherapy and vaccination is an important achievement for public health. Immunization with Bacillus of Calmette-Guerin (BCG) vaccine is done in 64 countries in the world and has been suggested to others (Briassoulis *et al.*, 2005). Immunization against tuberculosis can significantly assist prevention of the disease and decrease its fatality rate in children although it is not the same in adults (Understanding Positive PPD Skin Tests after BCG Vaccination, 2003).

BCG vaccination is done at birth in some countries including Iran but in some others it is administered when children enter primary school and at puberty. Many studies support BCG vaccination in school age.

Recently, World Health Organization (WHO) has recommended BCG vaccination at the age of 3 months, as a part of Expanded Program of Immunization (EPI) (Briassoulis *et al.*, 2005).

Indeed, the immunogenicity of BCG vaccine is under question, its efficacy is known to be dependent on the quality of its production, transport and injection techniques. The preventive effects of BCG vaccine has been repetitively studied in the world, its rate of immunogenicity in older children and adults has been shown to be 77% in United Kingdom, while 14% in South of USA but ineffective at all in Madras-India. In one study on 22 children with tuberculosis of vertebral column in developing countries, they had a positive history of BCG vaccination and its scar (Briassoulis *et al.*, 2005).

A metanalysis study by Colditz and coworkers in Boston-USA showed that BCG vaccination decreases the risk of tuberculosis up to 50% (Colditz *et al.*, 1994). BCG vaccination results in a delayed type hypersensitivity to tuberculin which can be measured by intradermal injection of Purified Protein Derivative (PPD). This hypersensitivity may be used as a test to evaluate everyone's immune response to previous BCG vaccination or for screening of tuberculosis. The cutaneous reaction to PPD is measured

by diameter of indurated area of skin, 48 to 72 h after its intradermal injection and interpreted as negative (Non-reactive) if the greatest diameter of induration is less than 5 mm and positive (reactive) if it is 10 mm or more. The results equal to 5 through 9 mm are construed as suspicious. The PPD test remains variably positive for a variable number of years since BCG vaccination (Rowland *et al.*, 2006).

Scholten's study on PPD test in New York showed that tuberculosis was rare in children entering primary schools despite of its tripled incidence in general population between 1978 and 1992. Besides, in everyone whose test became positive, it was found to be due to vaccination (Scholten *et al.*, 1999). A study in Barcelona-Spain showed that two BCG vaccinations in neonatal period and school age sustain the tuberculin test, positive for 20 to 25 years. They found that an indurated area larger than 15 mm in diameter can not rule out its vaccinal origin and recommended that a booster dose of BCG vaccine should be injected in those children whose PPD test has become negative after previous vaccination (Miret-Cuadras *et al.*, 1996).

Some studies on Native American and Eskimos of Alaska which included a follow up period of 50 to 60 years showed that a single dose of BCG vaccine in neonatal period has been 52% more effective than placebo (Aronson *et al.*, 2004).

According to above mentioned discrepancies in results of different studies on PPD test, we decided to carry out a research program on the results of this test in 7 to 8 years old children who had received a neonatal BCG vaccine and compare its findings with the results of a similar study on 3 months old infants, which has been done in year 2003, by author.

MATERIALS AND METHODS

In a comparative study from September 2005 to May 2007, we selected 150 children at the age of 7 to 8 years by simple random sampling from primary schools in different parts of Tabriz (Iran). They belonged to different socioeconomic classes and all of them had a BCG scar. Exclusion criteria applied for case selection were as followings: lack of a BCG scar, present malnutrition according to Gomez and Waterloo malnutrition criteria (Suraj and Gupte, 1998) and positive history of any vaccination or acute febrile illness since one month prior to study.

At first, the largest diameter of BCG scar was measured in millimeter and recorded for every selected child. Then 0.1 mL of 5-unit-PPD solution (a product of

Razi Institute-Iran) was injected intradermally at volar surface of left forearm by insulin syringe in such a manner that a small papule about 6 to 10 mm in diameter appeared at injection site.

Seventy two hours later, the largest diameter of indurated area generated by PPD injection, measured in millimeter and recorded. Then statistical analysis was done to compare the PPD-tests results with measurements of neonatal BCG scars, by using SPSS software, t-test and Chi-square.

RESULTS AND DISCUSSION

One hundred and fifty children were included in this study; 94 males (62.7%) and 56 females (37.3%), all of them had a BCG scar, from 1 to 11 mm in the largest diameter (Table 1).

The largest BCG-scar was 11 mm in diameter which was seen only in one girl. In general, there were BCG-scars with the size of 8 mm or more in 34 girls (60.7%) and 14 boys (15.95%), this difference is statistically meaningful and shows that BCG scars are larger in girls than in boys ($p = 0.007$).

The average size of BCG-scar was 7.03 mm in girls, 5.45 mm in boys and 6.05 mm for all cases.

Unless for one boy who had an induration area at PPD-injection site with a diameter of 8 mm, all other children had a PPD induration of 5 mm or less. Therefore we found that PPD-test reaction is less than 5 mm in 95.33% and 5 mm or more in 4.66% of all 150 studied cases. Positive PPD-test reaction which defined as an induration area with a diameter of 10 mm or more was not seen in any children in this study. The average size of induration reaction to PPD test was 2.3 mm in girls, 1.8 mm in boys and 1.99 mm for all cases.

Table 1: The frequency of different sizes of the largest Diameter of observed neonatal BCG-scars and indurated areas as PPD-test result in 150 studied children

Size (mm)	No. of children		
	Male	Female	Total
----- (%) -----			
Neonatal BCG scar			
1-3	10 (6.66)	2 (1.33)	12 (8)
4-6	54 (36)	30 (20)	84 (46)
7-9	15 (10)	24 (16)	39 (26)
≥10	4 (2.66)	11 (7.33)	15 (10)
Total	83 (55.3)	67 (44.6)	150 (100)
PPD-test results			
0	13 (8.66)	5 (3.33)	18 (12)
1-4	78 (52)	47 (31.3)	125 (83.33)
5	2 (1.33)	4 (2.66)	6 (4)
>5	1 (0.66)	0 (0)	1 (0.66)
Total	94 (62.6)	56 (37.3)	150 (100)

Table 2: Comparison of the frequency of different PPD-test results in two age groups after neonatal BCG vaccination

PPD-test result (the largest diameter of indurated area)	Age		p-value
	3 months old	7-8 years old	
No reaction	7 (4.66%)	18 (12%)	< 0.001
1 to 4 mm	61 (40.66%)	125 (83.33%)	
5 to 9 mm	70 (46.66%)	7 (4.66%)	
10 mm or more	12 (8%)	0 (0%)	
Total	150 (100%)	150 (100%)	

No child with a BCG scar sized 4 mm or less showed a PPD-test reaction sized 5 mm or more. 4.8% of children with a BCG scar sized 5 to 8 mm had a PPD-test reaction sized 5 mm or more. 11.11% of children with a BCG scar sized 9 mm or more had a PPD-test reaction sized 5 mm or more.

In general, all children who showed PPD induration sized 5 mm or more already had a BCG scar sized 5 mm or more.

This study revealed that during primary-school age (7-8 years old), the larger the size of neonatal BCG scar, the more frequent the PPD-test reaction size will be 5 to 9 mm. Statistical tests showed that there is a meaningful direct correlation between sizes of BCG scar and PPD-test reaction ($r = 0.21$, $p = 0.008$). As showed in Table 1, there was no child in this study whose PPD-test induration area reaches 10 mm or more.

This study on 150 children, at the age of 7 to 8 years, who had received BCG vaccination in neonatal period, showed that PPD-test resulted in induration area sized less than 5 mm in 95.33% (no induration in 12%) and 5 mm or more in 4.66% (maximum size was 8 mm in just one case 0.66%).

In another study carried out by author on the size of induration area resulted from PPD-test in 150 infants, 3 months after neonatal BCG vaccination, PPD-test reaction was less than 5 mm in 45.33% and 5 mm or more in 54.66% of infants (Sakha and Aghae, 2003).

Comparing the frequency of different sizes of PPD-test results in two age groups after neonatal BCG vaccination shows a significant statistical difference ($p < 0.001$).

This means that positive PPD (tuberculin) reaction induced by BCG vaccination decreases with increasing age and finally disappears (no induration in 12% of cases) (Table 2). One study in Saudi Arabia on 5 years old children showed that there was no difference in results of PPD test between BCG-vaccinated children (during neonatal period) and unvaccinated ones (Al-Kassimi *et al.*, 1991).

In USA, some studies showed that there is no difference in PPD (Mantoux) test reaction between

BCG vaccinated and unvaccinated persons (Ballew and Becker, 1995).

In one study carried out in Montréal-Canada, on persons between 10 and 25 years of age, it was revealed that result of PPD test was positive in 7.9, 18 and 25.4% among who has been vaccinated at infancy, 1-5 and 7 years of age, respectively. Therefore these Canadian researchers believe that the final effect of neonatal BCG vaccination looks like no vaccination (Menzies and Vissandjee, 1992).

Joncas study in Canada showed that in children above one year of age, who has received BCG vaccination during neonatal period, if PPD-test reaction is more than 10 to 12 mm in diameter, it must be related to natural infection by *M. tuberculosis* or other atypical Mycobacteria, but not to vaccine (Joncas *et al.*, 1975).

Furthermore, studies in Botswana in 1996 on children between 3 and 60 months of age, who has been vaccinated during neonatal period, cleared that those children who showed induration reaction larger than 10 mm to Mantoux test, had tubercle disease (Botswana, 1996).

Leung study in Hong Kong tried to determine the need for BCG vaccination in school-age children, which showed that PPD-test reaction was 10 mm or more in 1.93% of girls and 1.41% of boys in this age group (Leung *et al.*, 2005).

A study by Ildirim *et al.* (1995) in Turkey on children between 6 and 12 years of age, showed that the average diameter of PPD-test induration area was 14.8 ± 4.3 mm in children who possess 3 scars of BCG vaccination, but it was 6.3 ± 7.8 in children who possess one. Therefore, they recommended more than one BCG vaccination in those developing countries where tuberculosis is highly prevalent.

A similar study in Santiago-Chile, on 208 university students who had been vaccinated with BCG at birth and in 6 and 14 years of age, resulted in similar findings as mentioned above (Sepulveda *et al.*, 1990).

CONCLUSION

Overall, according to health progressions in developing countries for prevention of common preventable diseases and upon two studies by author in two sections of time and similar studies in other countries, it is recommended that a booster dose of BCG vaccine must be administered in children entering primary schools to increase and lengthen the efficacy of neonatal BCG vaccination.

REFERENCES

- Al-Kassimi, F.A., A.K. Abdullah, I.O. Al-Orainey and A.B. Benar *et al.*, 1991. The significance of positive Mantoux reactions in BCG-vaccinated children. *Tubercle*, 72 (2): 101-104.
- Aronson, N.E., M. Santosham, G.W. Comstock and R.S. Howard *et al.*, 2004. Long-term efficacy of BCG vaccine in American Indians and Alaska natives. *JAMA.*, 5, 291 (17): 2086-2091.
- Ballew, K.A. and D.M. Becker, 1995. Tuberculosis screening in adults who have received bacilli Calmette-Guerin vaccine. *South Med. J.*, 88 (10): 1025-1030.
- Botswana, 1996. Tuberculin skin test survey in a pediatric population with high BCG vaccination coverage. Botswana. MMWR Morb Mortal Wkely Report, 46 (36): 846-851.
- Briassoulis, G., I. Karabatsou, V. Gogoglou and A. Tsorva, 2005. BCG vaccination at three different age groups: Response and effectiveness. *J. Immune Based Ther. Vaccines. Apr.*, 1, 3 (1): 1.
- Colditz, G.A., T.F. Brewer, C.S. Berkey and E. Wilson *et al.*, 1994. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA.*, 271 (9): 698-702.
- Ildirim, I., M. Hacimustafaoglu and B. Ediz, 1995. Correlation of tuberculin induration with the number of Bacillus Calmette-Guerin vaccines. *Pediatr. Infect. Dis. J.*, 14 (12): 1060-1063.
- Joncas, J.H., R. Robitaille and T. Gauthier, 1975. Interpretation of the PPD skin test in BCG-vaccinated children. *Can. Med. Assoc. J.*, 26, 113 (2): 127-128.
- Leung, C.C., W.W. Yew, C.M. Tam, C.K. Chan, K.C. Chang and W.S. Law *et al.*, 2005. Tuberculin response in BCG vaccinated school children and the estimation of annual risk of infection in Hong Kong. *Thorax*, 60 (2): 124-129.
- Menzies, R. and B. Vissandjee, 1992. Effect of bacilli Calmette-Guerin vaccination on tuberculin reactivity. *Am. Rev. Respir. Dis.*, 145 (3): 621-625.
- Miret-Cuadras, P., J.M. Pina-Gutierrez and S. Juncosa, 1996. Tuberculin reactivity in Bacillus Calmette-Guerin vaccinated subjects. *Tuberc Lung. Dis.*, 77 (1): 52-58.
- Rowland, K., R. Guthmann, B. Jamieson and D. Malloy, 2006. Clinical inquiries, How should we manage a patient with a positive PPD and prior BCG vaccination? *J. Fam. Pract.*, 55 (8): 718-720.
- Sakha, K. and M. Aghaee, 2003. A survey on PPD-test results after BCG vaccination and its correlation with BCG scar in infants of Kermanshah province-Iran. *Med. J. Tabriz Univ. Med. Sci.*, 25 (1): 34-38.
- Scholten, J.N., P.I. Fujiwara and T.R. Frieden, 1999. Prevalence and factors associated with tuberculosis infection among new school enterans, New York City, 1991-1993. *Int. J. Tuberc Lung. Dis.*, 3 (1): 31-41.
- Sepulveda, R.L., X. Ferrer, C. Latrach and R.U. Sorensen, 1990. The influence of Calmette-Guerin bacillus immunization on the booster effect of tuberculin testing in healthy young adults. *Am. Rev. Respir. Dis.*, 142 (1): 24-28.
- Suraj and Gupte, 1998. The short textbook of pediatrics. Nutritional Deficiency States, pp: 115-116.
- Understanding Positive PPD Skin Tests after BCG Vaccination, 2003. http://www.pamf.org/patients/bcg_ppd.html.